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Influence of Substitution in the Benzene Ring on Optical Activity: Menthyl esters of di-methylamino, amino, and hydroxy benzoic acids and the Octyl phthalates.

Thesis for the Degree of Doctor of Philosophy.

by

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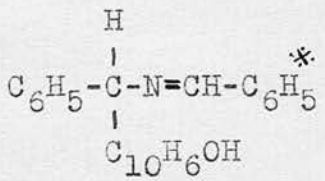
Introduction.

In recent years a considerable amount of work has been carried out in connection with the influence of substitution on the rotatory power of Optically Active compounds.A definite relationship has been found between the effect that such substituents have on physical properties, such as velocity of reaction,acidity and dielectric constants,and the effect that the same substituents have on the optical activity of the parent compound.

Betti,in a series of experiments recorded in the Gazzetta Chimica Italiana,[1] prepared a long series of Schiff's bases of the type



obtained by condensing β-Naphthol-benzylamine with substituted benzaldehydes and in which the phenyl group marked * was substituted in various ways.He prepared mono,di,and tri substituted compounds.

1. Betti,Gazzetta Chimica Italiana,1923.,53, 417.

Betti examined the optical activity of these derivatives and arranged the substituent groups in the order in which they affected the rotatory power. For example, in the ortho compounds his results gave the series

NO_2, Me, Cl, OH, H,

the rotations of the compounds falling as we pass from left to right. The para substituted compounds on the other hand gave the series

NO_2, Cl, H, Me, OH, OMe, .

Here again the rotation of the parent compound falls as we proceed from left to right in this series. Betti then examined the acidity of benzoic acid which had been substituted in a similar manner to the phenyl group in his optically active compounds, and on arranging the substituent groups in the order in which they affect the acidity he obtained a series which was in close agreement with that found for the rotatory powers. In the case of both the ortho and the para compounds the acidity becomes less as we pass from left to right along the series. Betti was unable to extend these results satisfactorily to other series of compounds.

Cohen[1] has prepared a large number of optically active compounds derived from menthol and the substituted benzoic acids.

1. Cohen and Dudley, J.C.S., 1910, 1732.
   See also Tschugaeff, Ber., 1898, 31, 1775.

He examined the rotatory power of these esters and although he pointed out that the values vary strongly with the nature of the substituent and its position in the ring he did not show that there is any relation between the effect of the substituent on the rotatory power and its influence on any other physical or chemical property of the compound.

Rule[1] has drawn attention to the fact that there is a very marked relationship in this case between the orientation effect of a group on benzene substitution and its effect on optical activity. For example, in the mono substituted menthyl benzoates it has been found that a substituent in the ortho position may either raise or lower the rotation of the parent compound. The substituent groups have been arranged in order, to form a series corresponding to their effect on rotation. It has been shown that a meta directive group raises the rotation, whereas an ortho-para directive group lowers the rotation. It has also been shown that the above series agrees very closely with the

1. Rule., J.C.S., 1927, 54.
   Rule and Smith, J.C.S., 1925, 2188.
   Rule and Paterson., J.C.S., 1924, 2155.
   Rule and Mitchell., J.C.S., 1926, 3202.

relative influence of the different groups on benzene substitution.

The following table shows the " ortho effect", that is to say the parallel which can be drawn between the influence of substituents in the ring on the nitration of these mono substituted benzenes and the influence of the same substituents on the optical activity of the Menthyl and Octyl ortho-benzoic esters.

In the table (a) represents the percentage of meta compound formed on nitration,(b) the percentage of para compound formed,(c) the molecular rotation of the menthyl esters and (d) the molecular rotation of the octyl esters.[1]

	NH_3^+	NO_2	COOH	COMe	H	Me	I	
a	Chiefly meta	93	76	55	-	3.1	-	
b		0.4	1.2	-	-	41	66	
c	-	381	332	261	239	231	237	
d	-	122	90-117	-	78	68.1	44.3	

	Br	Cl	F	COO^-	OMe	$N(Me)_2$.	
a	0.3	-	0.2	mostly ortho & para.			
b	62	70	87				
c	205	195	194	180	148	101 @	
d	49.2	47	-	-	33	-	

1. Rule,Hay,Numbers,and Paterson,J.C.S.,1928.,178.

@. This is the figure quoted by Cohen and Dudley J.C.S.,1910.,1737.,but it is shown in this thesis that the correct figure is 212 (in alcohol, c = 4.746) thus placing the $N(Me)_2$ group between Iodine and Bromine.

In the case of the menthyl esters the series is very complete and shows that there is a steady drop in the molecular rotation as we proceed from groups which are strongly meta directive to those which are strongly ortho-para directive in benzene substitution.

Further work by Rule and Smith[1] on the menthyl esters of the mono substituted acetic acids shows that if the substituent groups are arranged in order of their effect on optical activity a series is obtained which is very similar to that representing the influence of the same substituents on molecular inductive capacity,[2] and also to the series representing the effect of this substitution on the acidity of acetic acid. This type of influence is usually referred to as the general polar effect of the substituent.

In the case of meta and para substitution in the benzene ring, the influence on optical activity appears to be governed in a similar manner by the general polar effect. This effect is particularly well marked in the case of the octyl benzoates.[3]

1. Rule and Smith., J.C.S., 1925., 117, 2188.
2. Rule and Paterson., J.C.S., 1924, 125 2155.
3. See also Betti, loc.cit., on substituted Schiff's bases in which the general polar effect is observed in ortho, meta and para positions.

The general effect of the substituent is supposed to be due to a shift of the valency electrons away from an electro positive group such as CH_3 and towards an electro negative group such as NO_2, Cl, COOH. This leads to a progressive change in the rotation as we pass from left to right in the following series of para substituted octyl benzoates (in which, however, the expected positions of CH_3 and H are reversed).

$$NO_2 > COOH > OMe > Cl > CH_3 > H .$$

A good example of this effect is also given by the velocity of hydrolysis of the substituted benzyl chlorides.[1] In this case the series

NO_2, COOH, halogens, H, Me.

holds irrespective of the position of the substituent in the ring. With some exceptions the same general series has been shown to hold in the case of the dielectric constants of a number of aliphatic and aromatic compounds.[2]

There are several possible methods by which the influence of a group in an optically active compound may be communicated to the asymmetric atom.

1. Olivier, Rec.Trav.Chim., 1923., 42, 516, 775.
2. Rule and Paterson., J.C.S., 1924., 125, 2155.

The influence may be transmitted through space as in the well known 5th.carbon effect and possibly in the above ortho effect,[1] or it may be transmitted through the intervening chain of atoms.On the other hand,it is also probable that the asymmetric atom is influenced by the presence of such groups in other molecules,whether in neighbouring asymmetric molecules or in molecules of the solvent in which the rotation is measured. Some evidence in support of this last possibility is given by the figures showing the rotations of the sec-β-octyl esters of the monosubstituted acetic acids in various solvents.[2]

The order in which the substituents affect the rotation of the homogeneous esters is given by the series

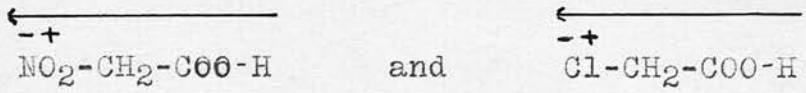
H>Me>OMe>Cl>Br>I.

Whereas the influence of the substituents, when present in a solvent of the type C_6H_5X, on any one of these esters is given by the series

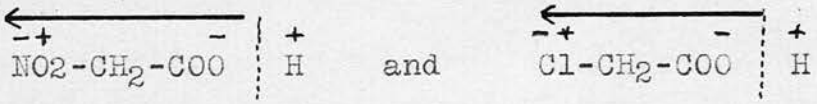
Me<H<OEt<Cl<Br<I.

1. Rule,Hay and Paul, J.C.S. 1928 (in the press.)
2. Rule and Mitchell.,J.C.S. 1926.,3202.

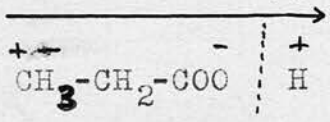
The mechanism of the general polar effect has been explained as being due to an electron shift caused by the presence of a dipole grouping. In the case of the monosubstituted acetic acids, the nitro or chloro compound may be represented as follows



The positive end of the dipole attracts electrons along the chain more than the distant negative end repels them. There is therefore an electron shift from right to left as indicated, which tends to assist ionisation.



In the case of the methyl group we have a shift in the opposite direction, and so the reverse effect is obtained, the substitution tending to diminish ionisation by hindering the transfer of the hydrogen electron to the oxygen atom

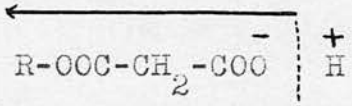


It appears that when the electron shift is away from the asymmetric atom in the menthyl and octyl esters of substituted acetic acids the rotation of the compound rises. A similar shift should occur also in the para substituted octyl benzoates, for example, and should therefore lead to a similar change in rotation. This has recently been shown to be the case.[1]

1. Rule, Hay, Numbers and Paterson. (loc.cit.)

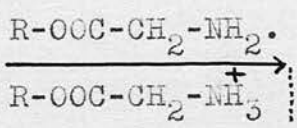
In this way we should be able to predict the effect on the rotation of a compound produced by the ionisation of a suitable grouping.

Consider an ester of the type



where R is an optically active residue. Whatever the state of affairs in the original unionised ester, the ionisation of the carboxyl group would be expected to lead to a further electron shift from right to left, that is towards the asymmetric atom, due to the repulsion exerted by the negative charge on the oxygen atom. One would expect a drop in the rotation under these conditions, if one compares the case with that of the above mentioned acetic and benzoic esters.

In the case of the amino group the reverse change takes place



In the presence of hydrochloric acid ionisation will occur, producing an electron shift away from the asymmetric atom. In this case one would expect the rotation to rise.

One may sum up the situation by saying that if, as most certainly appears to be the case, optically active compounds are affected by the

polar character of the substituent group, then it is probable that pronounced changes in the rotatory power will occur if a definite electric charge is present on the group.

This can be tested by introducing a group which is an ionisable complex and therefore capable of assuming such a charge under suitable conditions. Such a complex is well known to have a definite influence on substitution in the benzene nucleus, the course of the reaction varying with the sign of the charge on the complex. For example, benzoic acid chlorinates in meta position, but an aqueous solution of sodium benzoate yields a mixture of ortho and para derivatives. Similarly, aniline, which normally substitutes in ortho and para positions, forms chiefly meta compound when it is nitrated in presence of an excess of concentrated sulphuric acid.

These effects may reasonably be expected to have some corresponding influence on optical activity and the theory of electron shifts on ionisation would be expected to hold equally well for the cyclic compounds as for the chain compounds.

It is interesting to note that, whereas substitution in meta and para positions affects the octyl esters to a very great extent, similar substitution in the corresponding menthyl esters

has little or no influence on the rotation of the compound. As yet no explanation has been forwarded to account for this.

In order further to test these theories and in particular the theory of electron shifts, a number of optically active esters of amino- and dimethylamino-benzoic acid, and also of the hydroxy benzoic acids and the phthalic acids have now been prepared and examined polarimetrically.

Apparatus used in measuring the Rotatory Power.

In this work the rotatory power of the optically active esters was measured in a Schmidt and Haensch polarimeter. This instrument was capable of carrying a two decimeter tube and was fitted with a set of direct vision eyepieces, which made it possible to take readings for the lines λ = .4358, .5461, .5893, and .6708.

In cases where a four decimeter tube was used the rotations were measured in an apparatus by Hilger, which was fitted up so that only the lines λ = .4358 and .5461 could be read.

The sources of light were a Cooper-Hewitt mercury vapour lamp for the violet and green lines. Carefully dried and powdered A.R. sodium chloride heated in a meker burner in a platinum boat supplied the sodium flame and the lithium line was obtained by burning lithium carbonate in an oxy-coal gas flame.

For the measurements of rotatory power in the homogeneous state a jacketed tube was used. Through this was passed a constant current of water from the thermostat. The flow of water was kept

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circulating by means of a centrifugal water pump driven by a small electric motor. The lead tubes were well lagged with cotton wool and the temperature in the polarimeter tube remained constant within 0.1^{o} at all temperatures.

Solvents used in connection with this investigation.

Absolute alcohol.

Boiled over calcium filings and fractionated.

Benzene.

A.R.benzene,dried over sodium and fractionated.

Sodium ethoxide.

Prepared by dissolving carefully selected sodium in absolute alcohol and standardising by titration with hydrochloric acid,using methyl red as indicator.No solution was used after it was twenty-four hours old and in the majority of cases it was used as soon as it had been prepared.

Alcoholic hydrochloric acid.

Prepared by passing well dried hydrogen chloride gas into absolute alcohol well cooled in ice.The solution was standardised with caustic soda and used at once.

Piperidine.

This was supplied by the B.D.H.and used without further purification.

Pyridine.

B.D.H.sample used without further purification.

Thionyl chloride.

B.D.H. (purified.) used without further purification.

Preparative.

Resolution of Sec-β-octyl alcohol.

The optically active octyl alcohol used in this work was prepared from inactive sec-β-octyl alcohol (B.D.H.) by the method of resolution adopted by Pickard and Kenyon and later modified by Kenyon.[1]

Octyl alcohol (1 mol.) and phthalic anhydride (1 mol.) were heated together under reflux on an oil bath at 120° for twenty-five hours. In some cases excess of ethyl alcohol was added and the whole heated on the water bath for twenty minutes and the excess of ethyl alcohol distilled off, in other cases this part of the purification was omitted as it was found to be unnecessary. The object was to convert any unchanged phthalic anhydride into the ethyl ester and remove it as such with any unchanged octyl alcohol at a later stage. However it was found that it was better to remove the phthalic anhydride with the phthalic acid by filtration.

The contents of the flask were therefore poured into a solution of sodium carbonate and the aqueous octyl phthalate so formed extracted three times with petroleum ether to remove any traces of neutral esters, unchanged alcohol and ketonic impurities.

1. Pickard and Kenyon., J.C.S. 1907, 2058, & 1922, 2540.

It is found most important to extract thoroughly at this stage for if this is not done there is some difficulty later owing to the unchanged octyl alcohol preventing the ester from crystallising out. The alkaline aqueous solution was then made acid with the requisite amount of concentrated hydrochloric acid and the ester extracted with ether. The ethereal solution was then dried over sodium sulphate and the ether distilled off. The last traces of water and unchanged octyl alcohol were removed by distillation under reduced pressure. The inactive sec-β-octyl hydrogen phthalate so obtained was then recrystallised from petroleum ether (60 - 80°.) It was found that the best results were obtained by using one cc. of solvent for every gram of ester.

The ester was then dissolved in warm acetone and the calculated amount of brucine added. This operation has to be carried out quickly as it is necessary to get all the brucine into solution before the d-salt begins to crystallise out. This it begins to do almost as soon as the brucine has been added. It is therefore necessary to have the solution of the ester warm, add the brucine all at once and shake the flask well. The brucine then goes into solution almost immediately and after about two minutes the d-salt begins to separate. The solution was filtered at the pump, after having been allowed to cool. The d-salt was washed with a little acetone. The filtrate, which contained the l-enantiomorph

was poured into dilute hydrochloric acid, when the ester separated out as an oil, which soon solidified, the brucine remaining in solution as the hydrochloride. The laevo compound was filtered off, washed with water and dried.

The dextro compound was the dissolved in the minimum of hot ethyl alcohol and the solution poured into dilute acid. The d-ester was filtered off, washed with water and dried. Both the laevo and the dextro compounds were then recrystallised from 90% acetic acid until the rotations in 5% ethyl alcohol solution were constant and reached the value quoted by Pickard and Kenyon (loc.cit.)

The filtrates from the two salts were added together and made alkaline, when the brucine was precipitated with very little loss.

Dextro ester. 1.0502 g. in 20 cc. absolute alcohol gave a rotation of $+6.12^{\circ}$ in a two decimeter tube at 14° $\therefore [\alpha]_{4r} = +58.25^{\circ}$. /+

Laevo ester. 1.1718 g. in 20 cc. absolute alcohol gave a rotation of -6.79° in a two decimeter tube at 15.6° $\therefore [\alpha]_{4r} = -58.20^{\circ}$. /-

The pure octyl hydrogen phthalate was converted into the free alcohol in the following manner.

One molecular proportion of octyl hydrogen phthalate was added to two and a half molecular proportions of caustic potash dissolved in the minimum of water and the mixture boiled under reflux for four hours, after which the free alcohol was extracted with ether and the ethereal solution dried over sodium sulphate for several days. The solution was then filtered off. The active alcohol was fractionated under reduced pressure and the portion which always contains a certain amount of water, kept and worked up with any subsequent resolution of the alcohol.

The active alcohol boiled at 83°/ 20 mm.

In a one decimeter tube the alcohol gave a rotation of -8.14° for the sodium D line at 16°.

The l-Menthol used in this work was a sample from the B.D.H.(Recrystallised) and had a rotation of $[\alpha]_D = -49.39^{\circ}$

1.2628 g. in 25 cc. of absolute alcohol gave a rotation of -4.99° at 17.8° in a two decimeter tube.

Menthyl-o-dimethylamino-benzoate.

This compound was prepared after the method adopted by Cohen.[1] Some slight modifications have been introduced, especially in the purification of the menthyl ester.

Briefly, the method consists of the methy--ation of anthranilic acid to give the mono-methylamino acid. This was converted into the methyl ester, which was then methylated again to give the dimethylamino ester. On hydrolysis this gave the free acid, which was converted into the acid chloride by means of thionyl chloride. The acid chloride was then allowed to react with menthol to give the menthol ester.

Mono-methylamino-benzoic acid.

Anthranilic acid (137 g.) was dissolved in the equivalent amount of aqueous caustic soda (40 g. in 100 cc. of water). The solution was cooled in ice, and dimethyl sulphate added (126. g.) with vigourous shaking. After fifteen minutes the monomethyl acid began to separate. It was filtered at the pump and washed with water. A yield of 66% of the theoretical was obtained and the pure acid after recrystallisation from alcohol had the melting point, 177°.

Methyl-mono-methylamino-benzoate.

The above acid, well dried in vacuum

1. Cohen and Dudley, J.C.S., 1910., 1737.

was dissolved in three times its weight of methyl alcohol. The solution was heated on the water bath for 48 hours under reflux with a rapid current of dry hydrogen chloride. The reaction product containing the hydrochloride of the ester and any unchanged acid was then poured into an excess of sodium carbonate solution and the free ester floated to the surface as a grey viscid oil. This was extracted with ether and the ethereal solution evaporated down to half its bulk under diminished pressure. The remaining solution was dried over sodium sulphate for several days and the remainder of the ether removed. The ester was then distilled under reduced pressure. It distilled as a pale yellow oil, boiling point, 145 - 150°/ 28 mm. and solidified on cooling. It had a melting point of 15°. Yield, 60% of theoretical.

Methyl-di-methylamino-benzoate.

The ester obtained above was heated on the water bath with exactly one equivalent of methyl iodide. The reaction was carried out in a closely stoppered bottle, the stopper being wired in. Heating was continued for two hours. It is interesting to note that this reaction will proceed in the cold, but the reaction takes several days to go to completion. The hydriodide of the ester so obtained was washed at the pump with ether and was a pale yellow solid melting at 158°. It was added to the theoretical amount of sodium

carbonate solution and the free ester liberated. This was extracted with ether or benzene. The extract was dried over sodium sulphate and the solvent distilled off. The ester, which was a yellow oil, boiled at 145 - 147°/ 30 mm. and had very little odour. Unlike the mono methylamino ester it did not solidify on cooling. The yield was 100% of the theoretical.

o-Di-methylamino-benzoic acid.

The di-methylamino ester was boiled with water under reflux for twenty four hours. By the end of this time the ester had been hydrolysed and the contents of the flask were evaporated to dryness and the free acid extracted in a Soxhlet apparatus. The acid separated from the ethereal solution in pure white needles having a melting point of 72°. The yield was theoretical.

The preparation of the menthyl ester of this acid has presented much difficulty. This was apparently due to the slowness with which the acid chloride reacted with the menthol and to the difficulty experienced in separating the ester from the other products of the reaction.

o-Di-methylamino benzoyl chloride.

The acid chloride was prepared by boiling for an hour under reflux with excess of thionyl chloride.All traces of the excess thionyl chloride were then removed under reduced pressure by heating to 60° in a current of dry air.A reddish resinous mass resulted (see also Cohen,loc.cit.), which was heated for five hours at 120° with excess menthol.

Menthyl-o-di-methylamino benzoate.

The reaction between the menthol and the above mentioned acid chloride was carried out six times under what appeared to be exactly the same conditions,and in only one case did any marked reaction take place.On this occasion a vigourous evolution of hydrogen chloride occurred and the reaction was complete in a few minutes.The product was dissolved in the minimum of dilute hydrochloric acid and the solution extracted with ether in order to remove excess menthol.The acid solution was then made alkaline and the free ester extracted with ether.The ethereal solution was finally dried over sodium sulphate and the ether removed under reduced pressure.A highly coloured viscid mass was obtained.The rotation of this crude product was taken in benzene solution and then an attempt was made to purify the ester by Cohen's method.This consisted in dissolving the ester in ether and allowing

it to stand for several days over animal charcoal. The solution was filtered, the ether distilled off and the ester dissolved in light petroleum ether. The ester was then precipitated from this solution in the form of the hydrochloride with dry hydrogen chloride. The hydrochloride was then con--verted into the free ester with sodium carbonate and the ester extracted with ether asbefore. This method of purification did not alter the rotation of the compound and hence does not seem to effect any purification. Finally the following method was adopted.

The ester was distilled under high vacuum and after a few drops of low boiling liquid had come over it gave two main fractions, a pale yellow oil, which was distilled over at 170 - 171°/ 0.6mm. and a highly coloured residue , which was left in the flask. The residue in the flask was a glass of indefinite composition and contained nearly all of the coloured impurity. The pale yellow volatile oil solidified slowly on cooling, and its rotation was measured for the homogeneous state. This solid was recrystallised from light petroleum ether at - 15°, and was found to be completely soluble in dilute hydrochloric acid. It was a white solid having a melting point of 36 - 37° and gave the following analysis.

Analysis of menthyl-o-dimethylamino benzoate.

On combustion the compound gave the following analysis for carbon, hydrogen and nitrogen.

	Found	Required $C_{19}H_{29}O_2N$
Carbon	75.3%	75.2%
Hydrogen	9.90	9.64
Nitrogen	4.9	4.6

Measurements on the rotatory power.

The rotation of the crude compound before distillation was measured in 5% benzene solution. The volatile oil, which afterwards solidified, formed two thirds of the original mixture and it is noticable that if one compares the molecular rotation of the purified compound and the rotation of the residue left in the flask and then calculates the rotation which would be obtained from a mixture of these two fractions in the proportion in which they were present in the original mixture, the figure approximates to that obtained for the crude compound and to that obtained by Cohen (loc.cit.). The rotatory power of the pure ester was measured in the homogeneous state as mentioned above and then recrystallised from

petroleum ether. The rotatory power was then measured in benzene, alcohol, aqueous and alcoholic hydrochloric acid.

Owing to the fact that the ester solidified shortly after the determination of the rotation in the homogeneous state, the density of the compound was not determined.

The preparation of menthyl-o-dimethylamino benzoate has also been attempted from other points of view. It has not been found possible to prepare the ester by any of them.

In the above mentioned esterification by means of the acid chloride, pyridine was used to remove the hydrogen chloride from the reaction mixture, but this modification did not make any appreciable difference.

The menthyl ester of the monomethylamino acid has been prepared through the acid chloride and it was hoped that it would be possible to methylate this with methyl iodide. This however proved to be impracticable. It was also found possible to prepare the menthyl ester of the monomethylamino acid by direct esterification in presence of dry hydrogen chloride, but again it was found impossible to methylate the compound.

The menthyl ester of dimethylamino benzoic acid could not be prepared by direct esterification.

It has also not been found possible to prepare the acid chloride of anthranilic acid, (compare McMaster and Ahmann, J.A.C.S., 1928., 146.) nor can the menthyl ester of anthranilic acid be prepared by direct esterification.

In the preparation of the monomethylamino benzoic ester by direct esterification with menthol and dry hydrogen chloride a large quantity of menthene was obtained together with a yellow oil, which boiled at 150 - 180°/0.2 mm. This compound solidified and melted at 17 - 20° and appeared to have the required properties of the menthyl ester. Yield, 8% of the theory. The compound was not analysed nor was its rotatory power measured, since it was all used in an attempt to methylate it with methyl iodide.

Table I.

Rotatory Power of l-Menthyl o-dimethylamino-benzoate.

Solvent	c	l	α_{4358}	α_{5461}	α_{5893}	α_{6708}	$[M]_{4358}$	$[M]_{5461}$	$[M]_{5893}$	$[M]_{6708}$
Homogeneous State	–	0·5	–	43.97	35·67	25·74	–	–	–	–
Benzene	5·2430	1	–	–	3·56	–	–	–	205·9	–
Alcohol	4·7460	1	7·56	3·91	3·23	2·38	482·7※	249·6	206·2	150·7
Alcoholic HCl.equiv.	3·7360	1	5·94	3·60	3·09	2·36	481·8	292·0	250·6	191·4
Aqueous HCl.Normal	5·0060	1	7·41	4·43	3·79	–	448·4	268·2	229·5	–
Residue in benzene	2·1810	1	–	–	0·61	–	–	–	27·92	–

All rotations are laevo.

※ Owing to the high colour of the solution it was difficult to obtain a value for the violet.line. No significance is therefore attached to this figure.

m-Dimethylamino-benzoic acid.

The method used in the preparation of this acid was that due to Cumming.[1] This consisted in preparing the hydrochloride of the betaine, which on being carefully heated gave the methyl ester. The methyl ester was then hydrolysed with water to give the free acid.

m-Amino-benzoic acid (one mol.) was dissolved in the minimum of 50% methyl alcohol and treated with methyl iodide (three mols.) and caustic soda (one mol.). The solution was shaken in a mechanical shaker for two days and more soda added whenever the solution became acid, until a total of three molecules of soda had been added. The solution was then concentrated in order to remove most of the alcohol, and any dimethyl amino acid was removed by precipitation with acetic acid. The solution was filtered and the hydriodide of the betaine precipitated by the addition of hydrochloric acid. The hydriodide was recrystallised from water and melted at 180°. The hydriodide was carefully melted and hydrogen iodide evolved, the methyl ester of the dimethylated acid being left behind as a yellow oil. The contents of the flask were then heated with water and caustic soda and the free acid obtained by precipitation with acetic acid. Yield, 25% of the theory.

1. Cumming, Proc. Royal Soc., 78, Series A, 103.

An attempt was made to prepare the menthyl ester of this acid, which resulted in the production of a somewhat indefinite optically active compound. The method used was that of the acid chloride and the procedure was the same as in the case of the o-dimethylamino benzoate. The product was a glass and it was found impossible to purify it. A nitrogen estimation by Dumas method showed a nitrogen content of about twice the required value. It was thought that the compound had not been washed free from the pyridine used to assist the esterification. It was therefore dissolved in ether and the extract shaken out five times with dilute hydrochloric acid and then five times with water. The compound on recovery from the ethereal extract had exactly the same nitrogen content.

0.0995 g. of the compound on combustion gave 7.0 cc. of nitrogen at 17° and 756 mm.

Thus nitrogen found	=	8.3%
Required by $C_{19}H_{30}O_2N$	=	4.8

p-Dimethylamino-benzoic acid.

This acid was prepared by the method used by Johnston.[1] It consists in introducing both methyl groups with di-methyl sulphate.

p-Amino-benzoic acid (24 g.) was dissolved in one equivalent of 8% caustic soda and methyl sulphate (one mol.) was added. The mixture was well cooled and shaken. After one and a quarter hours the mono-methylated acid separated out as a pasty mass ,which was filtered off at the pump and washed with water. The monomethylamino acid was recrystallised from hot water and melted at 144 - 145°, and came out of solution in fine white needles, which turned slightly yellow on drying.

The monomethylamino acid so obtained was again methylated as above and the di-methylamino acid recrystallised from alcohol. It melted at 235 - 236°. The yield was nearly theoretical.

This acid was converted into the acid chloride by the method described by Fischer.[2] The acid chloride was a dark red crystalline substance (compare Cohen loc.cit.). The acid chloride was heated in the presence of pyridine with menthol for six hours at 140°, but no reaction took place.

1. J.Johnston., Proc.Royal Soc., 78 Series A,87.
2. E.Fischer., Ber.1905, 38.

An attempt was made to prepare the octyl ester of the p-dimethylamino acid. The acid chloride was heated with excess of optically active octyl alcohol. The mixture was heated for six hours at 140° under reflux and the reaction product extracted with ether and then separated from unchanged octyl alcohol in the usual manner. A highly coloured oil was obtained, which was optically active. As in the case of the menthyl ester of m-dimethylamino benzoic acid, however, the compound did not give a correct analysis. In spite of the fact that all traces of pyridine were removed the nitrogen content of the compound was very much too high.

0.2410 g. of the compound on combustion gave 23.7 cc. of nitrogen at 17° and 745 mm.

Thus the nitrogen found	11.3%
Required by $C_{17}H_{27}O_2N$	5.1

Menthyl p-dimethylamino-benzoate is described by Fischer & Hindley

At this stage it was decided that these compounds could not be prepared and attention was turned to the unsubstituted amino-benzoic acids with a view to finding some method of preparing their menthyl esters.

have attempts made to isolate the pure acid chlorides before interaction with menthol?

It is possible that sulphite-compounds were formed - if so, the reaction with menthol would be complicated

But distillation should in most cases decompose the sulphite-chlorides & the acid-chlorides desired -

A.McK.

Menthyl Anthranilate. (Menthyl-o-aminobenzoate.)

This compound was prepared by the reduction of Menthyl o-nitro-benzoate with tin and hydrochloric acid.

o-Nitro-benzoic acid (50 g.) was heated under reflux for several hours with excess of thionyl chloride until all the acid had dissolved. The excess of thionyl chloride was then dis-tilled off under diminished pressure and the acid chloride, without further purification, was mixed with three or four times its weight of menthol. The mixture was heated for several hours on the oil bath at 120° when a vigorous reaction set in with the evolution of hydrochloric acid gas.

The reaction products were dissolved in ether and the excess menthol removed by distillation in steam. The residue in the flask was then again extracted with ether, the ethereal solution well washed with water and dried over calcium chloride. After the removal of the ether, the solid ester was recrystallised from alcohol. The rotation of the nitro compound was measured in the homogeneous state at 100° and the specific rotation was found to be slightly higher than that obtained by Cohen.[1]

1. Cohen and Armes., J.C.S., 1905, 87, 1190.

The rotatory power of the compound was,

$$[M]_D^{98.0^\circ} = -125.44^\circ$$

whereas the figure obtained by Cohen was

$$[M]_D^{100^\circ} = -121.2^\circ$$

Further recrystallisation of the compound did not alter the rotation. The compound had a melting point of 62.5° and the yield was 48 g.

The optically pure ester (10 g.) was dissolved in alcohol (40 cc.), and tin (30 g.) and hydrochloric acid (35 cc. concentrated) were added. The solution was kept hot under reflux for half an hour. (The reduction appeared to be complete within ten minutes.) Slight evolution of gas took place. The solution was then diluted with water and filtered off from a slight metallic precipitate. The solution was then made alkaline until a permanent precipitate began to be formed. The slightly milky solution was then extracted with ether and the ethereal solution dried over sodium sulphate. The hydrochloride was precipitated as a bulky white precipitate on passing in dry hydrogen chloride. The hydrochloride was filtered off at the pump and washed with ether. Yield 12 g. This was dried in a vacuum desiccator over caustic potash and melted indefinitely at $152 - 176^\circ$. There was no sign of decomposition of the ester by hydrolysis at any stage.

The hydrochloride was recrystallised four times from alcohol, in which it is sparingly soluble. The compound was very slow in separating unless excess of hydrogen chloride was added. This probably indicates that the hydrochloride is dissociated to a considerable extent in alcoholic solution. As the hydrochloride tends to lose HCl on drying in vacuo, samples for rotational work were dried in vacuo over sulphuric acid in the presence of a small quantity of gaseous HCl. The labile chlorine in the compound was then estimated by titration in alcoholic solution in presence of nitric acid.

0.3113 g. of the hydrochloride required 10.16 cc. of 0.0988 normal silver nitrate.

Labile chlorine found	= 11.43%
Required for $C_{17}H_{26}O_2NCl$.	= 11.37%

The compound purified in this way was then converted into the free ester in the usual manner. This was also a solid, and melted at 62.5°.

A nitrogen estimation by Dumas method gave the following analysis.

0.1938 g. of the free ester on combustion gave 8.8 cc. of nitrogen at 14° and 753.3 mm.

Nitrogen found	= 5.3%
Required by $C_{17}H_{25}O_2N$.	= 5.1%

1-Menthyl m-amino-benzoate.

It has already been pointed out that it was found impossible to prepare this compound from the corresponding amino-benzoic acid and that the m-nitro-benzoic ester could not be reduced with tin and hydrochloric acid. Several experiments have been carried with a view to finding a suitable method of reduction for the nitro esters. The following method has been adopted.

Menthyl m-nitro benzoate (10 g.) was dissolved in absolute alcohol (200 cc.), the solution boiled under reflux, and a rapid current of CO_2 was passed into the flask until all the air had been dispelled. The theoretical amount of titanous chloride (15% solution) was added with excess of concentrated hydrochloric acid and the whole boiled until the titanous chloride had been decolourised. This took place after about four hours. A slight excess of titanous chloride was then added and the solution boiled for another hour. On cooling, caustic soda was added to the mixture so that the titanous hydroxide was not quite precipitated, and the majority of the amino ester extracted with ether. The solution was made completely alkaline and filtered off from titanous hydroxide. The precipitate was well washed with ether to remove any traces of amino ester and the filtrate also

extracted.The ethereal extracts were united and dried over sodium sulphate.The amino ester was precipitated as the hydrochloride by passing dry hydrochloric acid gas into the solution.In order for this operation to be sucessful it is nesessary that both the ethereal extract and the hydrochloric acid gas be very dry.(see note on hydrochlorides of amino esters,page 38).The oily hydrochloride was separated off from the ether,washed and converted into the free ester with sodium carbonate and extracted with ether.The ethereal extract was dried over sodium sulphate and the ether removed under reduced pressure.The ester was fractionated twice under high vacuum and distilled over as a practically colourless oil at 168°/ 1.8 mm.The yield after the first fractionation was 40% of the theoretical.

Analysis.

0.2004 g.of the ester gave 9.2 cc.of nitrogen at 18° and 750.0 mm.Hence

Nitrogen found	5.3%
Reqd.by $C_{17}H_{25}O_2N$	5.1%

l-Menthyl p-amino-benzoate.

This compound was prepared in a manner corresponding to that employed for the preparation of the meta compound.However it was found impossible to obtain the compound optically pure as it de--composed to a slight extent on distillation.On fractionation the ester distilled as a golden viscous oil at 175°/ 0.17 mm.,but the distillate always had a slight smell of free menthol.No method was found by which this free menthol could be removed and thus the rotational value obtained is in all probability somewhat lower than that of the optically pure compound.The compound formed a solid hydrochloride which melted at 180° and readily lost hydrogen chloride in solution to give the free ester.The yield after the first fraction--ation was 10% of the theoretical.

Analysis.

0.1923 g. of the ester gave 9.0 cc.of nitrogen at 17.0° and 755.0 mm.Hence

Nitrogen found	5.3%
Reqd.by $C_{17}H_{25}O_2N$	5.1%

Owing to the fact that the compound gives a good analysis it may be considered as being moderately pure and containing very little free menthol.

Note on the hydrochlorides of the amino esters.

In preparing these esters it was noticable that the hydrochlorides are comparatively unstable. They are not easily formed and they lose hydrogen chloride very easily. They are stable in concentrated hydrochloric acid, in which however the esters hydrolyse slightly, but at dilutions of hydrochloric acid below 8 N the free basic ester is precipitated. These properties led to considerable difficulty in the purification of the compounds as the only satis-factory method of freeing them from menthol and nitro ester is by shaking out an aqueous solution of the hydrochloride with ether or by precipitating as the hydrochloride from ether. Since concentrated hydrochloric acid solution always retains a considerable amount of the ether it is impossible to obtain a clean separation. The same difficulty has been experienced in the purification by precipitation with hydrogen chloride gas, as the precipitate, which in reallity consists of a very concentrated aqueous solution due to the presence of moisture in the ether, always retains some of the ether. Thus distillation is the only method of removing the last traces of unchanged nitro ester. It is interesting that the di-methylamino ester, which is a very much stronger base is soluble in 2 N hydrochloric acid.

Table II.

1-Menthyl amino-benzoates.

Solvent	Subst.	c	l	α_{4358}	α_{5461}	α_{5893}	α_{6708}	$[M]_{4358}$	$[M]_{5461}$	$[M]_{5893}$	$[M]_{6708}$
Alcohol	ortho	5·0090	1	9·31	5·70	4·76	3·66	511·0	312.9	261·3	209·9
Alcoholic HCl.Normal	ortho	5·0010	1	8·79	5·26	4·37	3·41	483·3	289·2	240·3	187·5
Alcohol	meta	3·186	1	5·40	3·25	2·76	2·11	466·1	276·4	238·2	182·1
Alcoholic HCl.Normal	meta	1·583	1	2·59	1·56	1·33	1·04	451·3	271·8	230·7	181·2
Alcohol	para	5·8930	1	9·00	5·54	4·64	3·53	405·0	259·0	217·5	164·2
Alcoholic HCl.Normal	para	4·7460	1	7·33	4·41	3·80	2·86	*425·0	255·0	219·0	165.5

All rotations are laevo.

* Owing to the high colour of the solution this value is only approximate.

l-Menthyl salicylate.

This compound was prepared from the acid chloride in the following manner.

Sodium salicylate (one mol.) was slowly added to thionyl chloride (one mol.), which was well cooled in ice. The reaction was vigourous and all the salicylate dissolved to give a glutinous like mass. This was extracted with petroleum ether and filtered at the pump to remove sodium chloride.

After removing the petroleum ether and any unchanged thionyl chloride under diminished pressure, an excess of menthol was added to the acid chloride, together with three molecules of pyridine and the whole heated on the oil bath to 120° for several hours. The reaction soon set in and a precipitate of pyridine hydrochloride appeared. The reaction mixture was washed with water to remove the pyridine hydrochloride and then steam distilled to remove excess menthol. The ester was then extracted with ether and the ethereal extract dried over sodium sulphate.

Two methods were used in the purification of the ester and the final product in each case gave the same molecular rotation. In the first place the ester was distilled under high vacuum.

It distilled over as a colourless oil at 156°/ 0.5 mm. The ester was twice fractionated and the rotation remained constant. Another sample of the ester was twice purified by dissolving it in warm methyl alcohol and precipitating by cooling it to -15°. The ester was separated washed and dried. It was distilled in the same manner as before and gave the same boiling point as the other sample and the same rotation. The yield after one fractionation was 60% of the theoretical.

Analysis.

	Carbon	Hydrogen.
Found.	73.86%	8.93%
Reqd. by $C_{17}H_{24}O_3$	73.91%	8.69%

Menthyl m-Hydroxy-benzoate.

This ester was prepared from the acid chloride of m-hydroxy benzoic acid, which was prepared from the sodium salt of the acid.

m-Hydroxy-benzoic acid (50 g.) was dissolved in one equivalent of sodium hydroxide solution. The solution was carefully evaporated to dryness, taking care not to raise the temperature above 50°. The sodium salt (60 g.) was well dried and added to two equivalents of thionyl chloride in small portions. The reaction was vigourous and the temperature was kept below zero until the reaction was finished. Excess of thionyl chloride was then removed under diminished pressure at 40°.

Menthol (44 g.) was added to the acid chloride with pyridine (2 mols.) and the whole heated for twenty four hours at 120°. It was impossible to get the reaction to go vigorously. The reaction products were diluted with water and extracted with ether, the excess menthol was then removed by steam distillation. However it was found that this treatment hydrolysed the ester and thereafter the excess menthol was removed by distillation in vacuo. The menthol distilled over at 100° at the water pump and the ester was then distilled under high vacuum. It distilled as a coloured oil at 182°/ 1.17 mm. Subsequent fractionation under the same conditions did not alter the

rotatory power of the compound. The ester did not solidify on cooling. Yield 20% of theory.

1-Menthyl p-Hydroxy-benzoate.

This ester was prepared in exactly the same way as the meta compound. That is to say, by forming the acid chloride from the sodium salt of the acid and then heating the acid chloride with menthol.

The excess menthol was removed as in the last case by distillation under the water pump vacuum and the ester itself distilled under high vacuum. As in the case of the meta ester the esterification did not proceed well and the yield was small, 10% of the theory. The ester distilled as a yellow oil at 178°/ 0.096 mm. It solidified to a transparent glass, but could not be obtained in the crystalline form. Subsequent fractionation under the same conditions as above did not bring about any change in the rotation.

Analysis.

menthol m-hydroxy-benzoate.

	C.	H.
Found	73.6%	8.8%
Required	73.9	8.7

menthol p-hydroxy-benzoate.

	C.	H.
Found	73.5%	8.9%
Required by $C_{17}H_{25}O_2$.	73.9	8.7.

Table III.

1-Menthyl Hydroxy-benzoates.

Solvent	Subst.	c ($d^{20} = 1.0467$)	l	α_{4358}	α_{5461}	α_{5893}	α_{6708}	$[M]^{20}_{4358}$	$[M]^{20}_{5461}$	$[M]^{20}_{5893}$	$[M]^{20}_{6708}$
Homogeneous	ortho	–	1	224.77	126.77	105.86	79.51	587.2	331.8	277.3	208.3
Alcohol	"	5.1630	2	18.70	11.16	9.46	7.17	500.0	298.75	252.9	191.6
Alcoholic ⁂ Caustic	"	4.8795	2	14.57	9.44	8.05	6.21	413.65	267.95	228.45	176.25
Piperidine	"	5.4455	2	19.63	11.29	9.51	7.21	499.3	287.05	241.9	183.35
Alcohol	meta	7.7350	1	–	7.46	–	–	–	266.2	–	–
Alcoholic ⁂ Caustic	"	5.6080	1	–	4.77	–	–	–	234.7	–	–
Piperidine	"	8.8150	1	–	7.08	–	–	–	221.6	–	–
Alcohol	para	5.1440	1	–	4.66	–	–	–	250.0	–	–
Alcoholic ⁂ Caustic	"	4.8730	1	–	4.25	–	–	–	241.2	–	–
Piperidine	"	4.2160	1	–	3.34	–	–	–	218.6	–	–

All rotations are laevo.

⁂ One equivalent of sodium ethoxide .

Table IV.

1-Menthyl Salicylate.(Homogeneous State).

Temperature	Observed Rotations.			
	α_{4358}	α_{5461}	α_{5893}	α_{6708}
15.2°	224.77	126.77	105.86	79.51.
46.8°	219.19	123.76	103.53	77.54
72.4°	213.66	120.83	101.22	75.71
94.2°	209.39	118.84	99.39	74.55.

Temperature	Density	Corrected Rotations				Molecular Rotations.			
		α_{4358}	α_{5461}	α_{5893}	α_{6708}	$[M]_{4358}$	$[M]_{.5461}$	$[M]_{.5893}$	$[M]_{.6708}$
20°	1.0467	223	126	105.3	79.1	587.2	331.8	277.3	208.3
40°	1.0319	218.4	123.3	103.2	77.3	584.1	329.8	276.0	206.7
60°	1.0170	215	121.5	101.7	76.2	583.4	329.8	276.0	206.8
80°	1.0022	211.7	120.0	100.4	75.2	583.0	330.6	276.5	207.1
100°	0.9877	208.6	118.0	99.2	74.3	583.0	330.9	277.2	207.6

All Rotations are laevo.

Sec-β-Octyl hydrogen phthalates.

Sec-β-Octyl hydrogen phthalate.

The preparation of this compound has already been described under the resolution of Octyl alcohol. The sample used in this work was dextro rotatory. The specific rotation of the sample was 58.25° for the mercury green line in a two decimeter tube, when the concentration was 5.251 % in absolute alcohol.

Sec-β-Octyl hydrogen terephthalate.

This compound was prepared after the method employed by Rule[1], using carefully purified terephthalic acid. The ester had a melting point of 95 - 96° and was recrystallised from ligroin. The sample used was dextro rotatory and had a specific rotation in acetone of 44.17°, for the sodium line.

Sec-β-Octyl hydrogen isophthalate.

This compound was prepared after the manner of the terephthalate, using isophthalic acid prepared by the oxidation of meta toluic acid with alkaline permanganate. The acid melted above 315°.

1. Rule, Hay, Numbers and Paterson, J.C.S., 1928., 183.

Isophthalic acid (21 g.) was heated under reflux with thionyl chloride (96 g.) for ten hours at 120°. Excess of thionyl chloride was removed under diminished pressure and the acid chloride distilled. It boiled at 187°/ 90 mm. and on cooling solidified to a white crystalline solid melting at 39.5 - 40.5°. It is not a liquid as stated by McMaster and Ahmann.[1]

The di-acid chloride, so obtained (14 g.) was heated with l-sec-β-octyl alcohol (17 g.) and pyridine (23 g.) under reflux for four hours at 130°. The reaction products were extracted with ether and the ethereal extract washed with water, dilute acid, water, sodium carbonate, and again with water. The ethereal solution was dried over sodium sulphate and the ether distilled off. The di-octylester was a liquid. yield 23 g. No attempt was made to distill it as it had been found that the corresponding ester of the terephthalate decomposed on distillation. The half hydrolysis was carried out in exactly the same manner as for the terephthalate, except that the emulsion was allowed to stand for a week and was then heated for twelve hours at 90°. It was impossible to isolate this compound free from octyl alcohol, owing to the readiness with which it hydrolysed when being worked up. A repetition of the experiment gave the same result.

1. McMaster and Ahmann. J.Am.C.S. 1928., 146.

Measurements of Rotatory Power.

In order to find out the effect of ionisation on the rotation of a compound it was decided to measure the rotation of the sodium salt of d-sec-β-octyl-hydrogen-phthalate in water and in alcohol at various dilutions, in so far as the solubilities of the compounds permitted.

d-Sec-β-octyl-hydrogen phthalate.

The sodium salt of this compound has not previously been examined. Two methods were employed which gave exactly the same results. A quantity of the salt was first prepared in the following manner. Twenty grams of octyl hydrogen phthalate was dissolved in the exact equivalent of caustic soda and the solution evaporated to dryness at a low temperature. If care was taken to use only one equivalent of caustic soda and evaporation was carried out below 50°, no hydrloysis took place. Twenty grams of the sodium salt were obtained.

Weighed amounts of this salt were used in the optical experiments carried out on the compound. The second method employed was to prepare the solutions for the polarimeter by using a weighed quantity of the free acid ester and adding to this the equivalent of a standard solution of caustic soda in alcohol or water according to the solvent used and then diluting up to the graduation mark.

d-Sec-β-octyl hydrogen phthalate.

The method used in this case was the second of the two methods described above. It was found that the sodium salt is very insoluble in absolute alcohol, and it was not possible to prepare a solution more concentrated than one per cent.

l-Menthyl hydroxy and amino benzoates.

The effect of ionisation on the rotation in the case of the hydroxy compounds was tested in a similar manner using a standard solution of sodium ethoxide.

The amino esters were tested with a standard solution of alcoholic hydrochloric acid. The method was checked in the case of the Anthranilate by using a weighed sample of the hydrochloride, which had been previously prepared. The rotatory power was the same in each case.

In all cases where the effect of ionisation was being tested in this way the rotatory power was measured immediately after the solution had been made up, so that there was very little risk of the compound being hydrolysed. The solutions were again tested after about an hour and only in a few cases was there any perceptible hydrolysis.

Wherever possible the rotations were measured for the four wave lengths.

Table V.

Sodium salt of d-Sec-β-octyl hydrogen phthalate.

Solvent	c	l	α_{4358}	α_{5461}	α_{5893}	α_{6708}	$[M]_{4358}$	$[M]_{5461}$	$[M]_{5893}$	$[M]_{6708}$	$\frac{\alpha_{vi}}{\alpha_D}$
Alcohol	0·9948	4	2·94	1·61	–	–	205·4	112·5	–	–	2·39
"	5·1585	2	6·02	3·28	2·66	1·97	158·6	83·35	71·65	55·55	2·26
"	15·5590	1	4·58	2·50	2·06	1·52	81·83	44·66	36·81	27·15	2·22
"	25·0265	1	9·05	5·19	4·35	3·33	100·5	57·5	48·32	36·98	2·08
Water	0·9876	4	3·38	1·89	–	–	237·6	133·0	–	–	–
"	5·2290	2	2·57	1·70	1·48	1·18	68·34	45·18	39·34	31·25	1·74
"	15·2940	2	−4·56	−1·10	−0·60	−0·19	−41·46	−10·03	−5·46	−1·73	7·62
"	29·9260	1	−10·60	−4·01	−2·86	−1·91	−98·42	−37·24	−26·57	−17·74	3·71

All rotations are dextro except where otherwise stated.

Table VI.

d-Sec-β-octyl hydrogen phthalate.

Solvent	conc.	$[M]_{5893}$
Alcohol	5.000	134°
"	20.00	131.5
"	30.00	129.5
"	36.80	128.6

The above table shows that there is a slight concentration effect in the case of the free acid ester. It will be seen that the Rotatory Power drops slightly as the concentration of the solution is increased.[1]

1. Rule, Hay, Numbers and Paterson., J.C.S., 1928, 178.

Table VII.

Sodium salt of d-Sec-β-octyl hydrogen terephthalate.

Solvent	c	l	α_{4358}	α_{5461}	α_{5893}	α_{6708}	$[M]_{4358}$	$[M]_{5461}$	$[M]_{5893}$	$[M]_{6708}$	
Alcohol	0·9932	4	3·66	2·12	–	–	256·0	148·3	–	–	–
Water	1·0150	2	2·32	1·23	1·00	0·76	317·7	168·5	136·9	103·9	2·32
"	2·5775	2	–	3·11	–	–	–	169·1	–	–	–
"	5·0290	2	11·49	6·21	5·18	3·77	317·6	171·6	143·2	104·2	2·22
"	14·5360	1	15·93	8·79	7·32	5·39	304·5	168·1	139·9	103·0	2·18

Discussion of Results.

It has been shown by the theory of " General Polarity " (see introduction) that if electrically charged complexes are introduced into the molecule of an organic compound, they should produce certain definite and even predictable changes in the physical and chemical properties of the compound. It is a well established fact that such complexes have a marked effect on the course of benzene substitution. This is the case with groups such as C_6H_5O and $C_6H_5COO^-$, which rapidly substitute in ortho and para positions.[1] Whereas ionised basic groupings of the type $-NR_1R_2R_3H$ have been shown by Vorländer[2] to direct the substituents into meta position.

This latter point has been confirmed by the work of Flürscheim and Holmes,[3] Ing and Robinson,[4] and also by Goss, Ingold and Wilson.[5]

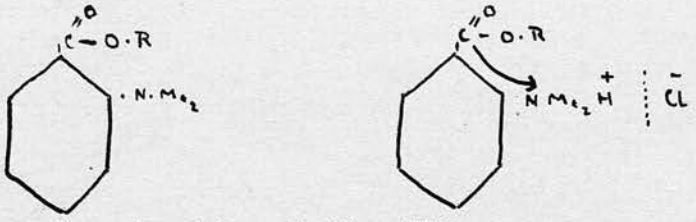
Ingold and Shaw[6] have explained the effect as being due in part to an influence of

1. Lossen, D.R-P. 146174.
2. Vorländer, Ber., 1919, 52, 263, 283.
3. Flürscheim and Holmes, J.C.S., 1926, 1563.
4. Ing and Robinson, ibid., 1655.
5. Goss, Ingold and Wilson, ibid., 2440
6. Ingold and Shaw, J.C.S., 1927, 2918. Ann.Rep.Chem.Soc., 1926, 129, et seq.

the general polar type and in part due to " tautomeric " electrical displacements.

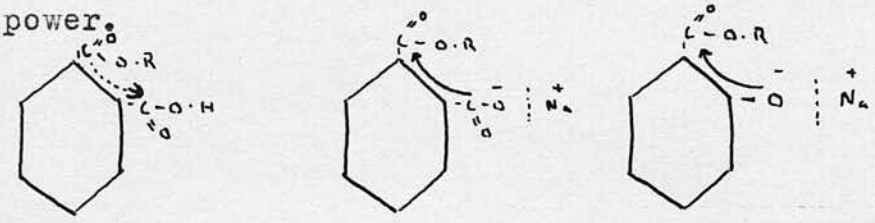
It has already been shown (see intr.) that there is a very marked connection between the power of orientation of a substituent in benzene substitution and its influence on the rotatory power,when such a substituent group is introduced into an optically active benzoic ester in the ortho position. One would therefore expect the effect of introducing a basic ionisable group into the ortho position to be that the rotation of the compound would be raised when such a complex is ionised. Whereas the introduction of a hydroxy or carboxy group would be to lower the rotation on ionisation.

Working along the lines of the general polar theory we come to the same conclusion.In the following case



although the general polarity of the NMe_2 group has not yet been definitely established,ionisation should result in an electron shift away from the asymmetric atom and towards the positively charged nitrogen atom. By comparison with the case of l-menthyl cyanoacetate one would expect a rise in the rotation.

In the case of the hydroxy compounds and the mono esters of the di-basic acids we have a different state of affairs on ionisation. Both the OH and the COOH groups increase the acidity of an acid and hence attract electrons towards themselves. Before ionisation therefore the electron shift due to the substituent is away from the asymmetric atom in the active ester, that is towards the free hydroxy or carboxyl group, thus leading to an increase in rotatory power.



In both cases the direction of the shift is reversed on ionisation and one might expect a drop in the rotation of the compounds under such conditions.

In the case of substitution in <u>meta</u> and <u>para</u> positions of octyl benzoate, the influence of the substituent group has been shown to be mainly of the general polar type. This is more particularly so in the <u>para</u> compounds. It would be expected that ionisation effects in these compounds would resemble those already predicted for the <u>ortho</u> compounds, although in a diminished degree as the length of the chain becomes longer. It has already been mentioned that in the menthyl benzoates the influence of substituents in <u>meta</u> and <u>para</u> positions is almost negligible.

The experimental results of the present investigation are summarised in the following tables, in which only the rotations for λ 5461 are given.

Table VIII.

1-Menthyl o-dimethylamino-benzoate.

Solvent	conc.	l	α_{5461}	$[M]_{5461}$
Alcohol	4.7460	1	3.91	249.6
(Menthyl benzoate in alcohol	5.0310	2	10.64	275.1)
Alcoholic HCl.equiv.	3.7360	1	3.60	292.0
Aqueous HCl.Normal	5.0060	1	4.43	268.2

On comparing the figures quoted for alcoholic solution it is seen that, the introduction of an O-NMe_2 grouping (which is ortho - para directive in type) into the molecule of menthyl benzoate leads to a fall in the rotatory power. This is changed to a rise in value when the basic group is ionised. The results are therefore in agreement with the demands of the polarity theory, and also with the influence of the substituents on benzene substitution.

Carboxylic esters.

Table IX.

Sodium salt of d-sec-β-Octyl hydrogen phthalate.

Solvent	conc.	l	α_{5461}	$[M]_{5461}$
Alcohol	5.1585	2	+3.28	+83.35
Water	5.2290	2	+1.70	+45.18

The value for the free ester in 5% alcohol solution is $[M]_{5461} = +161.94^{o}$

The values for the sec-β-octyl hydrogen phthalate are also in close agreement with prediction. The introduction of the COOH group raises the rotation, but on ionisation of the COOH group a considerable fall in the rotatory power occurs.

Table X.

Sodium salt of sec-β-octyl hydrogen phthalate.

Solvent	conc.	l	α_{5461}	M_{5461}
Alcohol	0.9932	4	2.12	148.3
Water	1.0150	2	1.23	168.5
"	2.5775	2	3.11	169.1
"	5.0290	2	6.21	171.6
"	14.5360	1	8.79	168.1

The free acid ester both in 5% and 1% alcohol solution is $[M]_{5461} = +145^{o}$.

The molecular rotations of the terephthalate however, show that in the para position the presence of the negative charge exerts little influence. The value for sodium octyl terephthalate is practically identical with that for the free ester. As the COOH group produces a considerable change in the rotatory power when introduced into the para position in octyl benzoate, the influence of the ionised group would have been expected to have been evident also. Possible the effect is here masked owing to some sort of interaction between the ions themselves. (See p. 64 on the influence of concentration.)

Hydroxy esters.

Table XI.

1-Menthyl hydroxy-benzoates.

Solvent	Substit.	conc.	l	α_{5461}	$[M]_{.5461}$
Homog.	ortho	($d.^{20} = 1.0467$)	1	126.0	303
Alcohol	"	5.1630	2	11.16	299
*Sod.ethox.	"	4.8795	2	9.44	268
Piperidine	"	5.4455	2	11.29	287
Alcohol	meta	7.7350	1	7.46	266
*Sod.ethox.	"	5.6080	1	4.77	235
Piperidine	"	8.8150	1	7.08	222
Alcohol	para	5.1440	1	4.66	250
*Sod.ethox.	"	4.8730	1	4.25	241
Piperidine	"	4.2160	1	3.34	219

*One molecular proportion of sodium ethoxide in alcohol.

In agreement with the theory, the rotatory powers of the ortho, meta and para compounds fall when measured for solutions in piperidine or in alcohol containing a molecular proportion of sodium ethoxide.

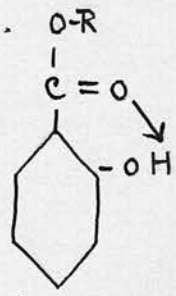
A surprising feature is the very high value obtained for the ortho hydroxy compound in the unionised state. This may possible be explained by recent work by Sidgwick[1] on co-ordination compounds. Sidgwick contends that in the ortho hydroxy benzoic acid and its esters the hydrogen atom of the hydroxyl group is co-ordinated with ketonic oxygen of the COOH group to form a chelate ring. He further points out that the tendency of such chelation is to prevent the individual molecules from associating with one another, as may still happen in the meta and para compounds. This leads to the ortho compound having a lower boiling point than its isomerides. In addition Sidgwick states that it is a characteristic property of liquid chelate hydroxy compounds, that they are less soluble in alcohol than the unchelated liquid isomeric forms. Both these tests point to the menthyl salicylate being of the chelated type. e.g.

	b.p.	Press.
Menthyl salicylate	156°	0.5 mm.
" m-hydroxy-benzoate	182°	1.2 mm.
" p-hydroxy-benzoate	178°	0.09 mm.

1. Sidgwick and Rubie, J.C.S. 1921, 1023.

The salicylic ester was found to be only sparingly soluble in methyl alcohol, although the para hydroxy ester was miscible in all proportions.

In the chelate compound the co-ordinate bond between the ketonic oxygen and the hydrogen atom is supposed to be a co-valent bond, both the electrons required for which are supplied by the oxygen atom. The net result is therefore to produce an electron transfer away from the asymmetric atom and as might be expected, this leads to an increase in the rotatory power.



The effect of ionising solvents on the hydroxy compound is of interest. Comparing table XI and looking at the figures obtained for the rotations in sodium ethoxide one sees that in all cases there is a considerable drop in the rotation but it is noticable that whereas there is a further drop in the case of piperidine in the meta and para compounds there is hardly any drop in the ortho compound with this solvent. One can only speculate as to the cause of this, but a possible explanation is based on the fact that the ortho compound is co-ordinated. If this is so and the chelate ring were capable of resisting the action of sodium ethoxide without being broken up there would be no change in the rotation on ionisation. It seems therefore that the chelate ring is broken up by the ethoxide and a resulting drop in the rotation

occurs, but not by the piperidine as there is no drop in this case. The meta and para compounds appear to be quite normal and follow the general effect.
It is interesting to note for the sake of comparison that the rotation of the unsubstituted benzoate does not change with the addition of even as much as four equivalents of sodium ethoxide and so the change cannot in any way be due to the formation of a sodium compound with the ester.
The rotatory power of l-Menthyl-benzoate in alcohol
$[M]_{5461} = -275.1^{\circ}$ $(\alpha = -10.64^{\circ}, \quad l = 2, \quad c. = 5.0310 \text{ g.})$
and in four equivalents of sodium ethoxide it was
$[M]_{5461} = -275.8^{\circ}$ $(\alpha = -10.60^{\circ}, \quad l = 2, \quad c. = 5.0010 \text{ g.})$
The rotation in this case dropped after about twenty minutes to 271.0°, this was in all probability due to hydrolysis. However this should be very much less where only one equivalent of sodium ethoxide was used and negligible in the cases of the hydroxy and the carboxy compounds, where the alkali is neutralised by the acidity of the ester.

Table XII.

l-Menthyl amino-benzoate.

Solvent	substit.	conc.	l	α_{5461}	$[M]_{5461}$
Alcohol	ortho	5.0090	1	5.70	313
Alcoholic HCl. equiv.	"	5.0010	1	5.26	289
Alcohol	meta	3.1860	1	3.25	276
Alcoholic HCl. equiv.	"	1.5830	1	1.56	272.
Alcohol	para	5.8930	1	5.54	259
Alcoholic HCl. equiv.	"	4.7460	1	4.41	255

Amino esters.

The high value obtained for the Anthranilic ester as compared with the dimethylamino ester again suggests that the compound is of the chelate type. This view is supported by the low boiling point of the ester as compared with the meta and para isomerides.

	b.p.	Press.
l-Menthyl Anthranilate	156	0.33 mm.
" m-amino-benzoate	168	1.80 mm.
" p-amino-benzoate	175	0.17 mm.

It will be seen that in the form of the hydrochloride the rotatory power of the ester is still higher than that of the menthyl benzoate,and is approximately the same as that found for the dimethylamino ester. This appears to show that the chelate ring is completely disrupted in acid solution.

The rotations of the meta and para esters differ little from that of the unsubstituted benzoic ester and undergo no change on ionisation.

These results confirm recent work by Pfeiffer,Angern and Wang[1] who have suggested that the keto group in the diketopiperazines co-ordinates with the primary and secondary amines but not with the tertiary amines,also with the primary and the secondary amino acids but not with the tertiary amino acids. The authors have examined the three isomeric dimethylamino benzoic acids and have found that they do not co-ordinate with the diketopiperazines

1.Peiffer Angern and Wang, Z.Physiol Chem.1927,164,182.

whereas the corresponding amino acids do so.

Influence of Concentration on Rotatory Power.

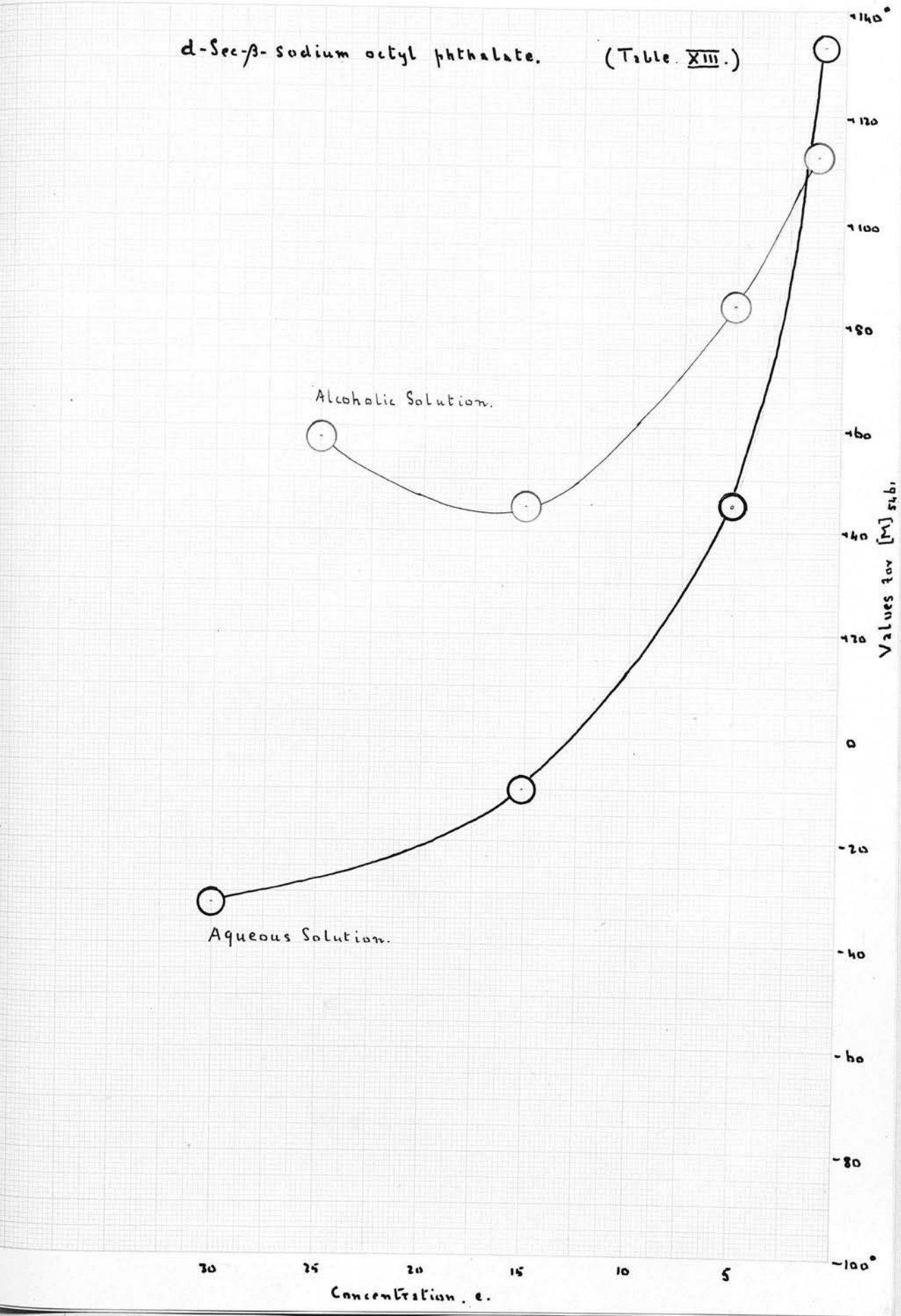
The effect of concentration on the rotatory power of the phthalates is very interesting although it is rather difficult to explain. The rotatory power of sodium octyl phthalate has been examined in different concentrations in alcohol and in water and the following table gives the results obtained.

Table XIII.

Sodium salt of sec-β-octyl hydrogen phthalate.

Solvent	conc.	l	α_{5461}	$[M]_{5461}$
Alcohol	0.9948	4	1.61	113
"	5.1585	2	3.28	83.4
"	15.5590	1	2.50	44.7
"	25.0265	1	5.19	57.7
Water	0.9876	4	1.89	133
"	5.2290	2	1.70	45.2
"	15.2940	2	- 1.10	- 10.0
"	29.9260	1	- 4.01	- 37.2

The rotatory power of the free acid ester in 5% alcoholic solution is $[M]_{5461} = 162.0^{\circ}$


d-Sec-β-Sodium octyl phthalate. (Table XIII.)
Alcoholic Solution.
Aqueous Solution.
+140°
+120
+100
+80
+60
+40
+20
0
-20
-40
-60
-80
-100°
Values for [M]5461.
30
25
20
15
10
5
Concentration. c.

d-Sec.-β-sodium-octyl-terephthalate. (Table X.)

Aqueous Solution.

Values for [M] 5461.

+180°

+160°

+140°

+120°

+100°

15 10 5 1

Concentration, c.

In the ortho compound (see diagram on p.63a.) it will be seen that there is a very rapid fall in the rotation of the salt as the concentration of the solution is increased. In the case of the compound in alcohol there is a minimum in the curve at 16.5% and after this the rotation begins to rise again. In the case of the compound in water the drop in the rotation on increased concentration is very much more sudden and at 14% there is a transition point and the rotation changes sign. The curve begins to flatten out again after this but there is no sign of any inflexion or minimum.

This points to some very powerful influence at work in the case of the ortho compound. Change in concentration has hardly any effect on the rotatory power of the para compound although there is a sign of a very small maximum. (see diagram p.63 b.) and table X.)

In the ortho compound one would have ex-pected the reverse to be the result of the increased concentration. If the rotation of the compound falls on ionisation one would expect the greatest drop in rotation to be at high dilutions where the ionisation is most complete. It may be that the abnormality is due to solvent influence or that the influence at work is some sort of interaction between the ions themselves, which may be associated at higher concentrations. In any case it is difficult to account for the reversal of sign and the minimum in the curve

for the alcoholic solutions. Similar inversions are observed with aqueous solutions of salts of certain other acids, e.g. tartaric and malic, although here there is no minimum value.

In conclusion my thanks are due to Dr.H.G.Rule to whom I am indebted for his very kind help and interest taken in the work during this investigation.

Summary.

1. The theory of General Polarity has been applied to the effect of ionisable complexes on the rotatory power of optically active benzoates and holds for ortho, di-methylamino, hydroxy and carboxy esters.

2. The ortho amino ester is a notable exception, which has been explained in view of recent work by Sidgwick on co-ordination compounds, and confirmed by evidence of boiling points and solubilities.

3. The exceptionally high value for the union-ised ortho hydroxy ester has also been explained by Sidgwick's work.

4. The meta and para compounds are unaffected by ionisation except in the case of the hydroxy compounds, the changes in which are governed by the general polar effect.

5. The concentration of the solution has a very marked effect on the rotatory power of the ionised Sodium sec-β-octyl phthalate. A very rapid drop in rotation accompanied by an inversion in sign taking place as the concentration rises. No satisfactory explanation can be advanced to account for this peculiarity.